REMARKS

Claim Amendment

After entry of the present amendment, claims 16, 18-22, 24-29, 43, 45-49, 51-55 and 79-84 are pending for the Examiner's review and consideration. Independent claims 16 and 43 have been amended to further recite the features of claims 23 and 50, respectively. Claims 23 and 50 have been canceled without prejudice. Since no new matter is introduced by these amendments, Applicants respectfully request their entry into the record of the present application.

Rejection Under 35 U.S.C. § 103(a) Should Be Withdrawn

Claims 16, 18-29, 43, 45-55, and 79-84 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Applicant's alleged admission that the method of using bupropion to treat smoking addiction and aid in smoking cessation is known, in view of Coutts *et al.*, *Chirality* 1:99-120 (1989) ("Coutts"). Applicants respectfully traverse this rejection.

As the Examiner is aware, three basic criteria that must be met to establish a case of *prima facie* obviousness. First, there must have been, at the time of the invention, a motivation to combine the references cited. Second, the alleged prior art must teach or suggest all of the limitations of the claims alleged to be obvious. Third, there must have been, at the time of the invention, a reasonable expectation of success. Manual of Patent Examining Procedure (August, 2001, "*MPEP*") § 2142. In contrast, an invitation to experiment or a contention that an invention is "obvious to try" does not render claims *prima facie* obvious, *see, e.g., Gillette Co. v. S. C. Johnson & Sons, Inc.*, 919 F.2d 720, 725 (Fed. Cir. 1990); *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988); *Jones v. Hardy*, 727 F.2d 1524, 1530; *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380 (Fed. Cir 1986) *cert. denied*, 480 U.S. 947 (1987) (prior art references were an invitation to try but did not show obviousness because they did not suggest how to accomplish the goal).

Further, as the Examiner is also aware, the requirement, in 35 U.S.C. § 103(a), "at the time the invention was made" is to avoid impermissible hindsight. *MPEP* § 2141.01. Thus, an Examiner "must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." *MPEP* § 2142. This is important, as "impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art." *Id.* Consequently, when determining whether or not a claimed invention is obvious, one must cast his "mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999).

Applicants respectfully submit that, in light of these principles, the Examiner has failed to establish a prima facie case of obviousness with regard to the present invention and that the rejections are based on impermissible hindsight.

The specification of the current application discloses that racemic mixture of bupropion is commercially available for the treatment of depression and achieve smoking cessation. *See, e.g.*, specification at page 2, lines 3-13. There is no suggestion in the prior art, nor any admission by Applicants, regarding the use of the (-)-stereoisomer of bupropion as presently claimed. Coutts, on the other hand, contains no disclosure regarding the use of (-) bupropion. All Coutts discloses is that different enantiomers of a compound may possibly possess different pharmodynamic properties. Regarding bupropion, Coutts merely discloses that racemic bupropion is a drug that possesses one chiral center and is used as an antidepressant. *See Coutts* at page 113, cols. 1-2. Moreover, Coutts does not disclose or suggest that enantiomers of bupropion have different pharmacological properties, much less that (-) bupropion is pharmacologically preferable over its (+) counterpart. Therefore, Coutts, alone or in combination with the disclosure in Applicants' specification, fails to disclose or suggest that (-) bupropion can be preferentially used to treat smoking addiction over its (+) counterpart, as presently claimed.

Furthermore, Applicants respectfully submit that, even if Applicant's statement could somehow be combined with Coutts, there would have been no reasonable

expectation of success, based on the disclosures, to achieve the present invention. This is primarily because, given the statement made by Applicants, the teachings of Coutts make it extremely difficult for one of ordinary skill in the art to pinpoint a candidate compound with a reasonable chance of success, and therefore would not motivate one of ordinary skill in the art to tackle such tasks. This is especially true when considering the following reasons.

First of all, there is no consistency in examples given in Coutts as to which enantiomer has better pharmacological properties. This is because the optical rotation of compounds in general has no direct correlation with their pharmacological activity. For example, the (-) enantiomer of thalidomide has been reported to be toxic (page 101, col. 1), whereas the (-) enantiomer of molindone is reported to be more useful than its (+) counterpart (page 106, col. 1). Furthermore, both enantiomers of some compounds are reported to be equally potent in their biological activity. For example, both enantiomers of 10-hydroxyamitriptyline have been shown to be "similar to one another in their abilities to inhibit NE and 5-HT uptake." *See Coutts* at page 116, col. 1. With these inconsistencies, all Coutts does is to provide a mere speculation that an enantiomer can be different, more harmful or beneficial. Therefore, one of ordinary skill in the art would not have any guidance from Coutts in picking out potential candidate that one enantiomer of which would show better pharmacological properties than the other.

Secondly, as Coutts itself states, there are numerous drugs which are administered as a racemic mixture. *See Coutts* at page 102, col. 1 ("In 1980, it was estimated that at least 398 drugs prescribed in the United States were racemic mixtures"). This would leave one of ordinary skill in the art with literally hundreds of potential candidates, from which he or she can attempt to separate out the optical enantiomers and test for the pharmacological properties of each enantiomer. Based on the inconsistencies disclosed in Coutts, one of ordinary skill in the art would not have expected a reasonable successful in any of the drugs.

Further, Applicants respectfully submit that a rejection of the pending claims can only be based on the use of impermissible hindsight, wherein the Examiner is using the claimed invention as a blueprint for the selection and combination of prior art. This is

particularly clear when one considers that there is no disclosure or suggestion in the prior art, or the present specification, of a method for treating nicotine addiction and aiding smoking cessation using (-)-bupropion that is substantially free of its (+)-stereoisomer, or greater than 90 % by weight of the total amount of bupropion, as presently claimed.

In the present case, racemic bupropion's known use as a drug that treats smoking addiction does nothing to motivate one of ordinary skill in the art to proceed with separating out each enantiomer of bupropion, considering the fact that bupropion is merely one of hundreds of compounds which were commercially available at the time of the invention. In other words, absent a specific teaching in the prior art that bupropion is a better candidate than other known racemic drugs for being a drug that one enantiomer of which is pharmaceutically more favorable than the other, selecting bupropion is as random as selecting, for example, deprenyl.

As the Federal Circuit has stated "The genius of invention is often a combination of known elements which in hindsight seems preordained. *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339 (Fed. Cir. 2001). Further, "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or modification to combine prior art references." *In re Dembiczak*, 175 F.3d at 999. This is because "[c]ombining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability - the essence of hindsight." *Id.* (citing *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138 (Fed. Cir. 1985). Moreover, the importance of casting the mind back to the time of the invention is to avoid "insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher." *In re Kotzab*, 217 F.3d 1365, 1369 (Fed. Cir. 2000). In light of these principles, Applicants respectfully submit that the Examiner's rejection of the pending claims is based on the use of impermissible hindsight.

For the foregoing reasons, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) should be withdrawn.

CONCLUSION

Applicants respectfully submit that all pending claims are now in condition for allowance, early notice of which is earnestly solicited. Should the Examiner disagree, a personal or telephonic interview is respectfully requested to resolve any remaining issues in this application.

No fee is believed to be due for the submission of this response, except the fee for the Petition for Extension of Time Submitted herein. Should any additional fee be required, however, please charge such fee to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

Date June 10, 2003

47,331
Beibing Gary Zhang (Reg. No.)

For: Anthony M. Insogna (Reg. No. 35,203)

PENNIE & EDMONDS LLP
1667 K Street, N.W.
Washington, D.C. 20006
(202) 496-4400

Enclosure

APPENDIX

The pending claims and status of all claims are as follows:

Claims 1-15. Canceled.

16. (currently amended) A method for treating nicotine addiction in a human suffering from nicotine addiction, which comprises administering to said human a therapeutically effective amount of (-)-bupropion, or a pharmaceutically acceptable salt thereof, substantially free of its (+)-stereoisomer, wherein the amount of (-)-bupropion or a pharmaceutically acceptable salt thereof is greater than approximately 90 % by weight of the total amount of bupropion.

17. Canceled.

18. The method of claim 16 wherein (-)-bupropion is administered intravenously, transdermally, or orally.

19. The method of claim 18 wherein (-)-bupropion is administered orally as a tablet or a capsule.

20. The method of claim 18 wherein the amount administered is from about 10 mg to about 750 mg.

21. The method of claim 19 wherein the amount administered is from about 50 mg to about 600 mg.

22. The method of claim 20 wherein the amount administered is from about 60 mg to about 450 mg.

23. Canceled. ~~The method of claim 16 wherein the amount of (-) bupropion or a pharmaceutically acceptable salt thereof is greater than approximately 90 % by weight of the total amount of bupropion.~~

24. The method of claim 16 wherein the amount of (-)- bupropion or a pharmaceutically acceptable salt thereof is 99 % or more by weight of the total amount of bupropion.

25. The method of claim 16 wherein the amount of (-)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its (+)-stereoisomer, is administered together with a pharmaceutically acceptable carrier.

26. The method according to claim 16 wherein (-)-bupropion is administered as the hydrochloride salt.

27. The method of claim 16 wherein (-)-bupropion is administered in a sustained or controlled release formulation.

28. The method of claim 16 wherein said nicotine addiction is an addiction to smoking, or chewing tobacco.

29. The method of claim 16 wherein said administration is made one to four times a day.

Claims 30-42. Canceled.

43. (currently amended) A method for aiding smoking cessation in a human who smokes, which comprises administering to said human a therapeutically effective amount of (-)-bupropion, or a pharmaceutically acceptable salt thereof, substantially free of its (+)-stereoisomer, wherein the amount of (-)-bupropion or a pharmaceutically acceptable salt thereof is greater than approximately 90 % by weight of the total amount of bupropion.

44. Canceled.

45. The method of claim 43 wherein (-)-bupropion is administered intravenously, transdermally, or orally.

46. The method of claim 45 wherein (-)-bupropion is administered orally as a tablet or a capsule.

47. The method of claim 43 wherein the amount administered is from about 10 mg to about 750 mg.

48. The method of claim 47 wherein the amount administered is from about 50 mg to about 600 mg.

49. The method of claim 48 wherein the amount administered is from about 60 mg to about 450 mg.

50. Canceled. ~~The method of claim 43 wherein the amount of (-) bupropion or a pharmaceutically acceptable salt thereof is greater than approximately 90 % by weight of the total amount of bupropion.~~

51. The method of claim 43 wherein the amount of (-)-bupropion or a pharmaceutically acceptable salt thereof is 99 % or more by weight of the total amount of bupropion.

52. The method of claim 43 wherein the amount of (-)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its (+)-stereoisomer is administered together with a pharmaceutically acceptable carrier.

53. The method according to claim 43 wherein (-)-bupropion is administered as the hydrochloride salt.

54. The method of claim 43 wherein (-)-bupropion is administered in a sustained or controlled release formulation.

55. The method according to claim 43, wherein said administration is made one to four times per day.

Claims 56-78. Canceled.

79. (previously added) The method of claim 45, wherein the (-)-bupropion is administered by bolus injection.

80. (previously added) The method of claim 45, wherein the (-)-bupropion is administered intrathecally.

81. (previously added) The method of claim 16, wherein the method avoids the concomitant liability of adverse effects associated with the administration of racemic bupropion.

82. (previously added) The method of claim 16, wherein the amount is sufficient to alleviate nicotine addiction, but insufficient to cause adverse effects associated with administration of racemic bupropion.

83. (previously added) The method of claim 43, wherein the method avoids the concomitant liability of adverse effects associated with the administration of racemic bupropion.

84. (previously added) The method of claim 43, wherein the amount is sufficient to achieve smoking cessation, but insufficient to cause adverse effects associated with administration of racemic bupropion.